DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 13, 2010 has been entered.

Withdrawn Rejections

The rejection of claims 35, 37-41, 43-46, 48-50, 52, 63 and 64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicant's amendments to the claims.

The rejection of claims 35, 37-41, 43-46, 48-50, 52, 63 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of applicant's amendments to the claims.

The rejection of claims 35-40, 42, 45, 50, 51, 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Voss et al. (WO 01/54719) has been withdrawn in view of applicant's amendments to the claims.

The rejection of claims 35-40, 42, 45, 50, 51 and 63 under 35 U.S.C. 102(b) as being anticipated by Voss et al. (Journal of Virology, 2003, 77(2):1049-1058) has been withdrawn in view of applicant's amendments to the claims.

The rejection of claims 35-42, 45, 50-52, 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Debrus et al. (WO 02/087614) has been withdrawn in view of applicant's amendments to the claims.

Claim Objections

Claims 35, 40 and 50 are objected to because of the following informalities: Claim 35 should delete the word “bound” before the phrase “exposed or available and thereby bound.” Claim 40 has a hard return after the g of glycine, and claim 50 should recite “is selected from.” Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 47, 69 and 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to, *inter alia*, peptides that are fragments, mutants or variants thereof.

The written description rejection is made because the claims are interpreted as being drawn to a genus of peptides recited as "fragments, mutants or variants thereof." The applicable standard for the written description requirement can be found in MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004).

While one would be able to construct fragments, mutants and variants of SEQ ID NO:2 and CD4 and test them for their ability to bind Tat and Env, respectively, this process of guesswork does not put one in possession of the genus of polypeptides used in the claimed complex. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is SEQ ID NO:2 and the structure/function of the polypeptides (capable of binding to Tat). For claim 47, the structure of CD4 is known in the art. There is no disclosure of any particular portion of either structure that must be conserved (or changed/mutated) in order to be "fragments, mutants or variants thereof" that interact as claimed. Further, the specification does not provide guidance for creating mutants or variants such that the fragments, mutants or variants still maintain the ability to bind their respective

proteins. Without proper guidance from the specification, one of ordinary skill in the art would not know where to mutate the proteins or how to create a variant of the protein while still maintaining the desired activity.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The court clearly states in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed. As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of "fragments, mutants or variants thereof." Given that the specification has only described the structure and function of SEQ ID NO:2, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

Response to Arguments

In the reply dated September 13, 2010, applicant states that the present claim amendments overcome the rejection. However, these amendments were not made in claims 42 and 47.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42, 47, 69 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42, 47, 69 and 71 recite "fragment, mutant or variant thereof." These terms are not defined in a manner such that one skilled in the art would know the scope of the claims. One would not know what type of "fragment, mutant or variant thereof" are encompassed by the claims or if a particular "fragment, mutant or variant" of Env or CD4 would be immunogenic or would be capable of binding the specified residues of SEQ ID NO:1 or Env, respectively. One of ordinary skill in the art would not know the metes and bounds of the claims.

Response to Arguments

In the reply dated September 13, 2010, applicant states that the present claim amendments overcome the rejection. However, these amendments were not made in claims 42 and 47.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-50, 52, 63, 64 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. (WO 01/54719) and further in view of Caselli et al. (J. Immunol., 1999, 162:5631-5638), Chang et al. (Vaccine, 1999, 17:1540-1548), Borbe et al. (Journal of Peptide Science, 1995, 1:109-123), Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al. (Virus Research, 1999, 60:159-169) and Watanabe et al. (Vaccine, 2000, 19(9-10):1199-1203).

The claims are directed to a complex comprising a first and a second peptide bound thereto, the first peptide comprising the V3 loop of gp120, and wherein the V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex, second peptide comprising the binding region which region comprises at least residues 21-40 and 46-58 of the Tat protein set forth in SEQ ID NO:1, or at least said residues with a further point mutation whereby Cys22 of Tat is replaced by Glycine to form a Tat22Cys22 mutant being capable of binding a region on gp120 comprising residues 301-419 of SEQ ID NO:2.

The instant claims do not recite the type of bond holding the complex components together. However, according to page 5 of the specification, the “complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. Whilst it is preferred, it is not necessary that the two species be present in stoichiometric amounts, nor that even a majority of either species be complexed or bound to the other.

All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Page 5 of the specification further states that "The complex of the present invention may rely simply on the natural interaction between Tat and the V3 loop of gp120. Weaker complexes may also be employed, but it is generally preferred to strengthen the complex. In this respect, for example, it is possible to employ the disulphide bridges that can occur in association with the cysteine-reach region of the Tat protein, or to use other protein cross-linking technologies that are known in the art such as, for example, the BS3 cross-linker." (emphasis added)

Voss et al. discloses the use of an HIV Tat protein and an HIV gp120 protein in the manufacture of a vaccine for immunization against HIV (abstract). In accordance with the teaching in the specification, Voss et al. discloses a combination of the two proteins, and a complex that relies simply on the natural interaction between Tat and the V3 loop of gp120 will form between the two proteins. Voss also discloses a kit comprising one or more of gp120, Nef and Tat proteins (see page 12).

Voss et al. does not teach use of a Cys22 Tat mutant, the use of the V3 loop as the first peptide (claim 41), gp120 V2 deletion mutants (claims 43 and 44), the addition of CD4 to the complex (claims 46 and 47), the addition of heparin sulphate to the complex (claim 48), the addition of other immune proteins (claim 49) or cross-linking the peptides (claim 52).

Caselli et al. teaches the use of Cys22 Tat mutants as immunogens. Caselli et al. teaches that because of the possible use of Tat as a component of an anti-HIV-1 vaccine (prophylactic and/or therapeutic) and considering the possibility that the long term expression and release of wild-type Tat in vivo may reactivate HIV-1 expression, Tat mutants that lack the ability to transactivate the HIV promoter (e.g., Cyss22 to Gly mutants) are good vaccine candidates (see page 5632). Caselli et al. found that the Tat mutants induced broad humoral and cellular responses (see, for example, the abstract and page 5632).

It would have been obvious to one of ordinary skill in the art to modify the immunogenic complex taught Voss et al. and use a Tat Cys22 mutant. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings and findings of Caselli et al. (if Tat is to be used as a vaccine, it should be mutated to eliminate the transactivation property while still maintaining the ability to induce immune responses).

It is well known in the art that the V3 loop is one of the most immunogenic peptides/fragments of gp120 (see, for example, Chang et al. and Borbe et al.). Thus, it would have been obvious to one of ordinary skill in the art to produce the vaccine composition of Voss et al. using Tat and known HIV Env proteins comprising the V3 loop of HIV (e.g., gp120, gp145 or gp160) or consisting of the V3 loop of HIV gp120. One would have been motivated to do so and there would have been a reasonable expectation of success as both proteins are known in the art as immunogenic and HIV

vaccine candidates. It also would have been obvious to cross-link the gp120 and Tat as cross-linking of vaccine antigens is common (see, for example, Watanabe et al.).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it also would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Voss et al. One would have been motivated to do so and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that

heparin sulfates facilitate the binding of HIV-1 to cells, which would cause the exposure of gp120 epitopes.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 35-50, 52, 63, 64 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. (Journal of Virology, 2003, 77(2):1049-1058) and further in view of Caselli et al. (J. Immunol., 1999, 162:5631-5638), Chang et al. (Vaccine, 1999, 17:1540-1548), Borbe et al. (Journal of Peptide Science, 1995, 1:109-123), Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al. (Virus Research, 1999, 60:159-169) and Watanabe et al. (Vaccine, 2000, 19(9-10):1199-1203).

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It is well known in the art that the V3 loop is one of the most immunogenic peptides/fragments of gp120 (see, for example, Chang et al. and Borbe et al.). Thus, it would have been obvious to one of ordinary skill in the art to produce the vaccine composition of Voss et al. using Tat and known HIV Env proteins comprising the V3 loop of HIV (e.g., gp120, gp145 or gp160) or consisting of the V3 loop of HIV gp120. One would have been motivated to do so and there would have been a reasonable expectation of success as both proteins are known in the art as immunogenic and HIV vaccine candidates. It also would have been obvious to cross-link the gp120 and Tat as cross-linking of vaccine antigens is common (see, for example, Watanabe et al.).

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Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and

there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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Debrus et al. discloses a vaccine composed of HIV-1 gp120 and Nef-Tat fusions or Nef and Tat. Debrus et al. teaches that the gp120 protein is the principal target of neutralizing antibodies, but unfortunately the most immunogenic regions of the proteins (V3 loop) are also the most variable parts of the protein. Therefore, the use of gp120 (or its precursor gp160) alone as a vaccine antigen to elicit neutralizing antibodies is thought to be of limited use for a broadly protective vaccine. The gp120 protein does also contain epitopes that are recognized by cytotoxic T lymphocytes (CTL). For this reason gp120 and gp160 are considered to be useful antigenic components in vaccines that aim at eliciting cell-mediated immune responses (particularly CTL). Non-envelope proteins of HIV-1 have been described and include for example internal structural proteins such as the products of the gag and pol genes and, other non-structural proteins such as Rev, Nef, Vif and Tat (see pages 1 and 2).

Debrus et al. also teaches preferred combinations of adjuvant and antigen comprise the HIV gp120 and Nef-Tat proteins in combination with QS2 1,3D-MPL in an oil in water emulsion and that the proteins can be cross-linked. Preferably the Tat, Nef or Nef-Tat act in synergy with gp120 in the treatment or prevention of HIV (see pages 14 and 17).

In accordance with the teaching in the specification (see page 5 of the specification), Debrus et al. discloses a combination of the two HIV proteins, and a complex will form between the two proteins that relies simply on the natural interaction between Tat and the V3 loop of gp120.

Debrus et al. does not teach use of a Cys22 Tat mutant, the use of the V3 loop as the first peptide (claim 41), gp120 V2 deletion mutants (claims 43 and 44), the addition of CD4 to the complex (claims 46 and 47), the addition of heparin sulphate to the complex (claim 48), the addition of other immune proteins (claim 49) or cross-linking the peptides (claim 52).

Caselli et al. teaches the use of Cys22 Tat mutants as immunogens. Caselli et al. teaches that because of the possible use of Tat as a component of an anti-HIV-1 vaccine (prophylactic and/or therapeutic) and considering the possibility that the long term expression and release of wild-type Tat in vivo may reactivate HIV-1 expression, Tat mutants that lack the ability to transactivate the HIV promoter (e.g., Cyss22 to Gly mutants) are good vaccine candidates (see page 5632). Caselli et al. found that the Tat mutants induced broad humoral and cellular responses (see, for example, the abstract and page 5632).

It would have been obvious to one of ordinary skill in the art to modify the immunogenic complex taught Voss et al. and use a Tat Cys22 mutant. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings and findings of Caselli et al. (if Tat is to be used as a vaccine, it should be mutated to eliminate the transactivation property while still maintaining the ability to induce immune responses).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

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include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells, which would cause the exposure of gp120 epitopes.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated September 13, 2010, applicant again argues that none of the cited references teach the necessity for the accessibility of the V3 loop nor do any of the references teach conditions which would make the V3 loop available for binding to Tat. Applicant's arguments have been fully considered but not found persuasive.

As noted above, the instant claims do not recite the type of bond holding the complex components Tat and gp120 V3 together. However, according to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. . . . All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Page 5 of the specification further states that "The complex of the present invention may rely simply on the natural interaction between Tat and the V3 loop of gp120. Weaker complexes may also be employed, but it is generally preferred to strengthen the complex. In this respect, for example, it is possible to employ the disulphide bridges that can occur in association with the cysteine-reach region of the Tat protein, or to use other protein cross-linking technologies that are known in the art such as, for example, the BS3 cross-linker." (emphasis added)

The cited references teach immunogenic compositions comprising Tat and gp120 with an intact V3 loop. Therefore, according to the teachings of the specification,

Tat and V3 of gp120 will naturally interact. This is an inherent feature of the prior art Tat/gp120 compositions, and according to §2112(II) of the M.P.E.P., there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.").

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is

(571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648